REMARKS

Claims 9-17 and 20-28 are withdrawn from consideration due to the restriction requirement issued on May 18, 2005. In this paper, Applicants have amended claims 2, 5, 6, and 7 to more precisely define the subject matter claimed. Support for the amendments to claim 2 can be found in original claim 1. Support for the amendments to claims 5, 6 and 7 can be found in original claim 8. No new matter has been added by the present amendments. In addition, claims 1, 3, 8, and 18 have been canceled.

Rejection under 35 U.S.C. §112, First Paragraph

Claims 2, 4-7, and 19 stand rejected under 35 U.S.C. §112, first paragraph, for referring to functional variants of the amino acid sequences disclosed, as well as for referring to helper epitopes. The Office Action held that there was an infinite number of functional variants of the sequences whose undisclosed structure did not correspond with their function, and that the structure of a helper epitope was not provided.

Because applicants have canceled claims 1, 3, 8, and 18, the rejections as to these claims are now moot. Applicants further respectfully submit that the specification fully supports the limitation "or functional variants thereof." Paragraphs [0024] through [0027] provide a detailed description of the functional variants encompassed by the present invention, how to obtain them, and how to test them for their immunostimulatory effect. All these procedures are well within the average skill in the art, requiring no more than routine experimentation. Provided below is a reproduction of paragraphs [0024] through [0027] which demonstrates the amount of guidance given in the specification to identify and isolate functional variants of the sequences disclosed:

> **[0024]** ...Thus, in a further preferred embodiment, the invention embraces functional variants of PTH-rP peptides. As used herein,

a "functional variant" or "variant" of a PTH-rP immunogenic peptide is a peptide which contains one or more modifications to the primary amino acid sequence of an immunostimulatory PTH-rP peptide while retaining the immunostimulatory effect disclosed herein. If a functional variant of a PTH-rP peptide involves an amino acid substitution, conservative amino acid substitutions typically will be preferred, i.e., substitutions which retain a property of the original amino acid such as charge, hydrophobicity, conformation, etc. Examples of conservative substitutions of amino acids include substitutions made among amino acids within the following groups: (1) M, I, L, V; (2) F, Y, W; (3) K, R, H; (4) A, G; (5) S, T; (6) Q, N; and (7) E, D. Binding of a variant PTH-rP peptide to the MHC molecule and stimulation of the T cell by the variant peptide presented by the MHC molecule indicates that the variant peptide is a functional variant.

[0025] Modifications which generate functional variants of PTH-rP peptides can may be made in order to enhance peptide stability in an expression system, to enhance the stability of protein-protein binding such as HLA-peptide binding, or to increase the avidity of T cell receptors. The amino acid residues of the PTH-rP peptide can be mutated according to the principles of MHC and T cell receptor contact points outlined above. Again, any method for preparing modified or variant peptides can be employed, such as synthesis of the modified or variant peptide or its recombinant production using a mutated nucleic acid molecule. The identification of additional or optimized immunostimulatory PTH-rP peptides may also include the step of comparing the stimulation of the T cell by the PTH-rP peptide and the stimulation of the T cell by the functional variant as a determination of the effectiveness of the stimulation of the T cell by the functional variant. By comparing the functional variant PTH-rP peptide with a known PTH-rP peptide, peptides with increased T cell stimulatory properties can be prepared.

[0026] The individual PTH-rP peptides may also have one or more amino acids added to either or both ends. Nested sets of MHC binding peptides have been identified, wherein the peptides share a core sequence but have different amino acids at their amino and/or carboxyl terminal ends. For example residues of the peptide which contact MHC pockets may be kept constant while other residues may be varied. Alternatively, specified amino acid substitutions may be prepared to generate functional variants of PTH-rP peptides which retain binding to MHC and T cell receptor. The binding of the PTH-rP peptide to the MHC molecule and stimulation of the T cell are then assessed according to standard

> procedures. For example, as exemplified below, the PTH-rP peptide can be contacted with an antigen presenting cell that contains the MHC molecule which binds the PTH-rP peptide to form a complex of the peptide and antigen presenting cell. This complex can then be contacted with a T cell which recognizes the PTH-rP peptide presented by the MHC binding molecule. T cells can be obtained from a patient suffering from a tumor expressing PTH-rP or from healthy subjects. Recognition of PTH-rP peptides or functional variants thereof by the T cells can be determined by measuring an indicator of T cell stimulation such as TNF or IFNγ production. Similar procedures can be carried out for identification and characterization of other PTH-rP peptides. Additional methods of selecting and testing peptides for MHC binding and T cell recognition are well known in the art.
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> **[0027]** Thus, methods for identifying PTH-rP peptides, and functional variants thereof, are provided. In general, the methods include selecting a PTH-rP peptide predicted to bind to a preselected MHC and/or stimulating a TCR, testing the binding of the PTH-rP peptide to an MHC molecule and generating T cells which are activated by the PTH-rP peptide presented by the MHC molecule. In a preferred embodiment, the PTH-rP peptide comprises any amino acid subsequence of SEQ ID NO: 1. In more preferred embodiments, the PTH-rP peptide comprises the amino acid sequence of SEQ ID NO:5. In another preferred embodiments, the PTH-rP peptide comprises the amino acid sequence of SEQ ID NO:3. In yet another much preferred embodiment, the PTH-rP peptide comprises any or all of the amino acid sequences of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5. These peptides can be used to generate PTH-rP specific T-cell responses with anti-tumor activity. For example, autologous antigen presenting cells can be isolated from a patient and treated to obtain cells which present PTH-rP peptide epitopes in association with both MHC (HLA) class I and II molecules. Thus, these cells are capable of stimulating both $CD4^+$ and $CD8^+$ cell responses.

Based on the substantial amount of guidance provided by the specification, a person of skill in the art can readily identify, isolate, test, make and use functional variants of the disclosed amino acid sequences. Accordingly, applicants respectfully request withdrawal of the rejection.

The Office Action further held that claim 4 did not satisfy the written description requirement for reciting a "helper epitope," the structure of which was allegedly not provided. Applicants respectfully disagree because the specification, at paragraph [0032] provides not only examples of helper epitopes well known in the art, but also specifically refers to disclosed SEQ ID NO:6, the HBV core antigen helper epitope, as well as to several publications, all incorporated by reference, that describe other well known helper epitopes in detail. Provided below is a reproduction of the relevant parts of paragraph [0032] which illustrates the detailed description of helper epitopes in the specification.

> [0032] ... Universal T helper epitopes are well known in the art and may be derived from HBV core antigen (SEQ ID NO: 6) tetanus toxoid, pseudomonas aeruginosa toxin A, beta-galactosidase, brucella abortus, keyhole limpet hemocyanin, influenza virus hemagglutinin and nucleoprotein, hepatitis B core and surface antigens, malaria circumsporozoite, ovalbumin, etc. Alternatively, or additionally, T helper motifs such as those described in O'Sullivan et al., J. Immunol. 147:2663-2669, 1991, may be included. Such multiepitope peptides are expected to exhibit increased immunogenicity by a variety of mechanisms, one of which is their processing into several epitopes which are recognized by multiple branches of the immune system for the generation of enhanced immune responses. Examples of multiepitope peptides can be found in Thomson et al., Proc. Natl. Acad Sci. USA 92:5845-5849, 1995; Heiser et al., J. Immunol. 164: 5508-5514, 2000 and Gilbert et al., Nature Biotechnol. 15:1280-1284, 1997, while universal, promiscuous, or multifunctional T cell epitopes are described in Calvo-Calle et al., J. Immunol. 159: 1362, 1997; Takeshita et al., J. Immunol. 154: 1973-1986; and Carreno et al., J. Immunol. 148: 894-899, 1992, among many other references known to those skilled in the art. Thus, multiepitopic PTH-rP peptides containing various numbers and combinations of epitopes can be prepared and tested for recognition by CTLs and for efficacy in increasing an immune response. By administering PTH-rP peptides which bind MHC class I and class II molecules an improved immune response may be provided by inducing both T helper cells and T killer cells.

Applicants respectfully submit that helper epitopes are not only well known in the art but that the specification additionally provides specific examples of helper epitopes suitable for purposes of the present invention. Accordingly, applicants respectfully request that the rejection be withdrawn.

Claims 1-8, and 18-19 have been rejected for allegedly failing to comply with the enablement requirement, however the basis of the enablement rejection appears directed entirely to the subject matter of claim 1, which has been canceled. For instance, the Office Action's analysis of the Wands factors refers exclusively to the "fragments of the amino acid sequence of SEQ ID NO: 1," previously recited in canceled claim 1. Accordingly, applicants have taken the enablement rejection of pending claims 2, 4-7, and 19 under advisement but respectfully defer responding until a clarification of the basis for the rejection with respect to the pending claims is received.

Rejection under 35 U.S.C. §112, Second Paragraph

Claim 19 stands rejected as indefinite for reciting a "kit." The Office Action held that the kit was not defined. Applicants respectfully submit that the specification, at paragraph [0035] provides a clear description of the kits encompassed by the present invention:

> **[0035]** In a preferred embodiment, the invention provides kits which allow the artisan to prepare a desired immunotherapeutic regimen. An example of a kit comprises any of the PTH-rP peptides of the invention, as well as multiepitopic PTH-rP fusion peptides including universal T cell epitopes and the functional variants previously discussed. The kit may also comprise virosomes loaded with the PTH-rP peptides of the invention, either by encapsulation or by surface-crosslinking. The kit may also include virosomes loaded with the nucleic acids coding for the PTH-rP peptides of the invention operably linked to regulatory sequences as previously described. The kit preferably includes

> instructions for use of the compositions. Other components may be added to the kits, as desired.

Accordingly, applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §102(b)

Claim 1 has been rejected as allegedly anticipated by Bagnoli et al. (US 5,880,093). Because applicants have canceled claim 1, the rejection is now moot as to this claim.

Claims 1, 2, 5, and 8 have been rejected as allegedly anticipated by EP 0 822 200 A1 ("EP"). Because claims 1 and 8 have been canceled, the rejection with respect to these claims are now moot. Claims 2 and 5 stand rejected under 35 U.S.C. §102(b) as being anticipated by EP, due to the alleged disclosure of SEQ ID NO:2 in claim 10 on page 67. Applicants respectfully submit that in order to anticipate a claim under 35 U.S.C. § 102, a reference must teach every element of the claim. See MPEP 2131. As the Court of Appeals for the Federal Circuit has held:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. [...] There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

Scripps Clinic Research & Foundation v. Genentech Inc., 927 F.2d 1585, 1576, Federal Circuit, 1991. Applicants respectfully submit that EP discloses an amino acid sequence which differs from SEQ ID NO:2. The sequence disclosed in EP contains three additional terminal (DKG) residues and is thus not the same as SEQ ID NO:2. Furthermore, the non-identical amino acid sequence disclosed by EP is described in the context of PTH and PTH-rP analogs containing a synthetic amphipathic alpha helix useful in the treatment of osteoporosis. No immunostimulatory effect is disclosed for any of the sequences described in EP. By contrast, claims 2 and 5 of the present invention are directed to immunostimulatory amino acid sequences

in the treatment of cancer. Because EP fails to disclose every element of pending claims 2 and 5 it cannot anticipate the claimed invention as a matter of law. Accordingly, claims 2 and 5 are novel over EP, and applicants respectfully request withdrawal of the rejection.

Claims 2 and 5 stand rejected under 35 U.S.C. §102(b) as being anticipated by Rosenblatt *et al.*, US Patent No. 5,114,843 ("Rosenblatt"). The Office Action held that SEQ ID NO:3 was disclosed in claim 2 of Rosenblatt. Applicants respectfully submit that claim 2 of Rosenblatt discloses a synthetic amino acid sequence containing a D-amino acid ($D\text{-}Trp^{12}$) followed by a 25-amino acid subsequence of human humoral hypercalcemia factor. SEQ ID NO:3, by contrast, is a 10 amino acid sequence which, by virtue of its length alone, cannot be identical to the sequence disclosed in Rosenblatt. Nor are the Rosenblatt sequences disclosed as having an immunostimulatory effect. Thus, Rosenblatt fails to disclose every element of the claimed invention and therefore cannot anticipate it as a matter of law. Accordingly, applicants respectfully request that the rejection be withdrawn.

Claims 2 and 5 further stand rejected under 35 U.S.C. §102(b) as being anticipated by WO 00/69900. The Office Action held that SEQ ID NO:4 and SEQ ID NO:5 were disclosed as SEQ ID NO:305 in WO 00/69900. Applicants respectfully submit that SEQ ID NO:305 is a 32-amino acid peptide that, again, by virtue alone of its different length from that of SEQ ID NOs:4 and 5, fails to disclose them identically. WO 00/69900 further fails to disclose any immunostimulatory effect for the sequences described therein, and thus cannot be anticipatory as a matter of law. Accordingly, applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. §103(a)

Claim 3 has been canceled, and thus the rejections as to this claim are now moot. Claim 4 stands rejected under 35 U.S.C. §103(a) as being unpatentable over EP in view of Yoneda, *et al.* The Office Action stated that EP discloses SEQ ID NO:2, but fails to teach a helper epitope. Applicants respectfully traverse the rejection. As discussed in the response to the 102(b) rejections, EP fails to disclose every element of claim 2 because the sequence it discloses is neither identical to that of SEQ ID NO:2 nor disclosed as having an immunostimulatory effect. Thus, EP neither anticipates nor suggests the elements of claim 2. Being dependent from claim 2, claim 4 incorporates all the elements of claim 2, adding a helper epitope. Because EP fails to anticipate or suggest the elements of claim 2, it likewise fails to anticipate or suggest the elements of dependent claim 4. The combination of EP with Yoneda does not change this, because Yoneda discloses only monoclonal antibodies raised against PTH-rP, preferably against the N-terminal region of amino acids 1-34. Yoneda neither discloses nor suggests any of the claimed immunostimulatory sequences of the present invention, nor does it address the use of helper epitopes as the defined in the present specification at paragraph [0032], discussed *infra*. Because the combined teachings of EP in view of Yoneda do not or suggest or render obvious the elements of claim 4, applicants respectfully request that the rejection be withdrawn.

Claim 4 further stands rejected as being unpatentable over WO 00/69900 in view of Yoneda. The Office Action stated that WO 00/69900 discloses SEQ ID NO:4 and SEQ ID NO:5, while Yoneda et al. teach a helper epitope. Applicants respectfully traverse the rejection for the same reasons as above. First, WO 00/69900 fails to disclose or suggest either SEQ ID NO:4 or SEQ ID NO:5, instead referring to a 32-residue peptide with no teaching of its

immunostimulatory effect. Yoneda, as discussed, supra, likewise fails to teach or suggest SEQ ID NO:4 or SEQ ID NO:5 and contains no disclosure of a helper epitope. Thus, the combined teachings of WO 00/69900 with Yoneda neither suggest nor render obvious the elements of claim 4, and applicants respectfully request withdrawal of the rejection.

Claims 5 and 6 stand rejected under 35 U.S.C. §103(a), as being unpatentable over Bagnoli *et al.*, as well as over Bagnoli in view of Yoneda. The Office Action held that Bagnoli discloses SEQ ID NO:1 and that it would have been obvious to one of ordinary still to place a few of these peptides together in a composition. Applicants respectfully traverse the rejection. Claim 5 has been amended to more clearly define the subject matter claimed and now recites an immunostimulatory peptide consisting of two or more amino acid sequences selected from the group consisting of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5. Claim 6 depends from claim 5 and specifies the arrangement of the sequences of claim 5. Bagnoli *et al.* neither teach nor suggest any of the sequences listed, nor do Bagnoli *et al.* disclose their immunostimulatory effect. As discussed previously, supra, Yoneda does not add any teaching, suggestion, or motivation to the disclosure of Bagnoli that would lead a person of skill to the immunostimulatory sequences presently claimed. Accordingly, applicants respectfully submit that claims 5 and 6 are novel and unobvious over Bagnoli and Yoneda, and that the rejection should be withdrawn.

Claims 18 and 19 stand rejected as being unpatentable 35 U.S.C. §103(a) over Bagnoli (for SEQ ID NO:1), EP (for SEQ ID NO:2), Rosenblatt (for SEQ ID NO:3), and WO 00/69900 (for SEQ ID NO:4 and 5). The Office Action stated that SEQ ID NO:1, 2, 3, 4, and 5 were disclosed by these references and thus their inclusion in a kit would have been obvious. Applicants respectfully traverse the rejection. Claim 18 has been canceled, and thus the rejection

as to it is now moot. Pending claim 19 depends from claim 2, and thus incorporates all the elements contained in claim 2. Because claim 2 is novel and unobvious over Bagnoli, EP, Rosenblatt, and WO 00/69900, for the reasons discussed supra, dependent claim 19 is also novel and unobvious over the references cited. Accordingly, applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested. If the Examiner has any questions, the Examiner is invited to call Applicants' representative directly at (212) 969-3000.

Respectfully submitted,

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